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NEW PROSTAGLANDIN ANALOGS AND METHOD FOR THEIR PRODUCTION

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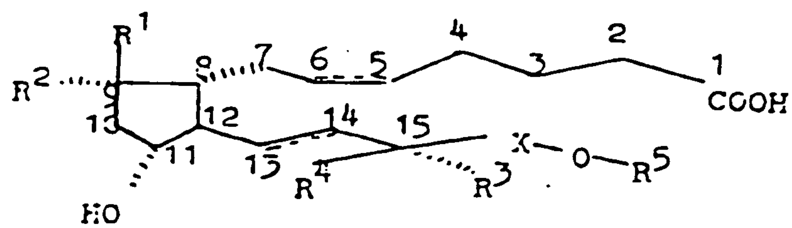
New prostaglandin analogs and method for their production

Prostaglandins are a group of natural substances that are isolated from various animal tissues. In mammals, they are responsible for a large number of physiological effects. The natural prostaglandins have a carbon structure of generally 20 C atoms and differ predominantly due to the larger or smaller number of hydroxyl groups or double bonds in the cyclopentane ring (with regard to structure and effect of prostaglandins, see, among others, M. F. Cuthbert, "The Prostaglandins, Pharmacological and Therapeutic Advances," William Heinemann Medical Books LTD, London 1973).

The synthesis of non-naturally occurring analogs of prostanoic acids, in which a large number of the pharmacological effects of the natural prostanoic acids are differentiated, is increasingly gaining in importance.

The invention under consideration concerns new, non-naturally occurring analogs of prostanoic acids of formula I:



which comprise both the optically active compounds of the natural configuration, as well as the racemic compounds, and in which the meanings are as follows:

R^1 and R^2 together are oxygen or, each hydrogen or a hydroxyl group, wherein R^1 and R^2 are different;

R^3 and R^4, are each hydrogen or a hydroxyl group, wherein R^3 and R^4 are different;

X is a straight-chain or branched alkyl radical with 1-5 C atoms, or a phenyl or benzyl radical, which can be substituted, 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms;

R^5, for the case in which X is a straight-chain or branched alkyl radical with 1-5 C atoms, is

a diphenyl ether, which is either unsubstituted or substituted, 1 to 3-fold, in one or both rings with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxy, each with 1-4 C atoms, or a phenoxyalkyl radical, unsubstituted in the ring or substituted 1 to 3-fold, with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms, wherein the alkyl radical is straight-chain and contains 2-5 C atoms, or is branched and contains 3-6 C atoms;

or for the case in which X is a substituted or unsubstituted phenyl radical, is

a benzyl radical, which can be substituted 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxy, alkyl, and/or alkoxyl, each with 1-4 C atoms;

or for the case in which X is a substituted or unsubstituted benzyl radical, is

a phenyl radical, which can be substituted 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms;

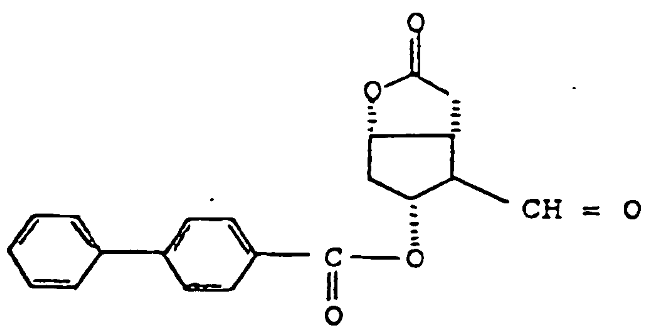
and wherein C atoms 5 and 6 and 13 and 14 are bound, either all by single bonds or all by double bonds, and their physiologically compatible salts with organic and inorganic bases

and their esters with aliphatic, cycloaliphatic, or arylaliphatic alcohols with 1-8 C atoms.

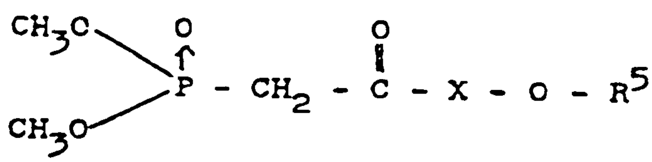
The invention also concerns a method for the production of new, non-naturally occurring analogs of prostanoic acids of formula I, their physiologically compatible salts, their esters and pharmaceutical preparations which contain them as active substances.

The method is characterized by the fact that

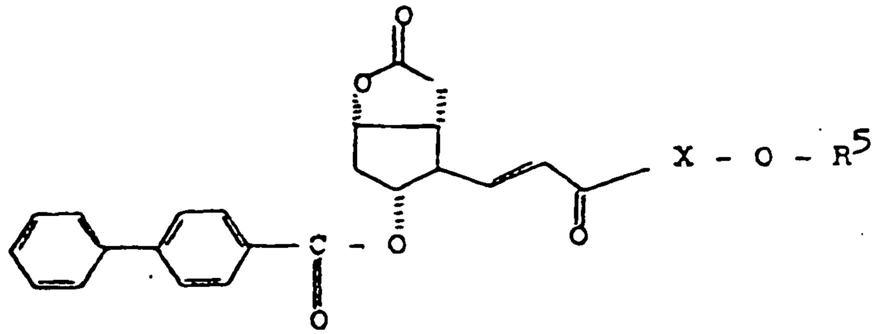
a) the aldehyde of formula III



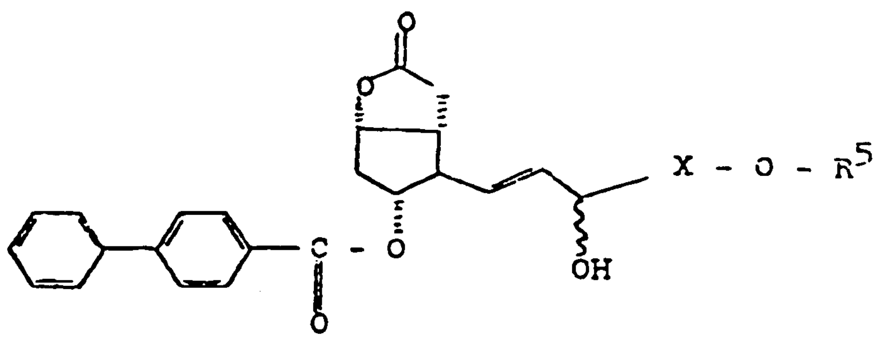
is reacted with a phosphonate of formula IV:



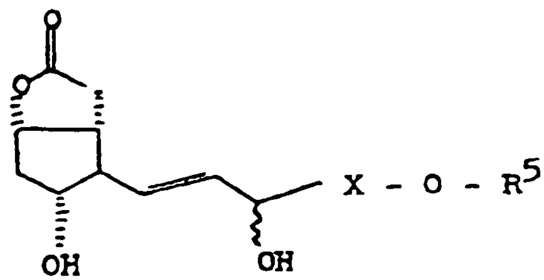
wherein X and R^5 have the same meaning as in formula I, to form an unsaturated ketone of formula V:



b) the obtained ketone of formula V is reduced with a complex metal hydride to form the epimeric mixture of alcohols of formula VI:

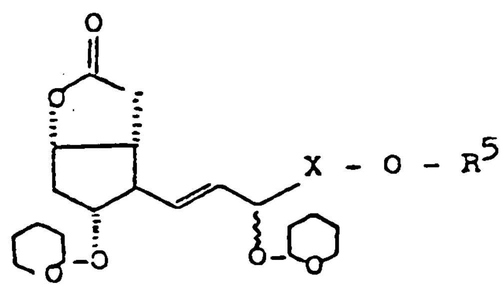


wherein X and R^5 have the same meaning as in formula I;
c) the alcohol of formula VI obtained as an epimeric mixture or after separation of the epimers, as a pure S- or R-epimer, is converted into a diol of formula VII with an anhydrous alkali metal or alkaline-earth metal carbonate in an alcoholic medium at room temperature:



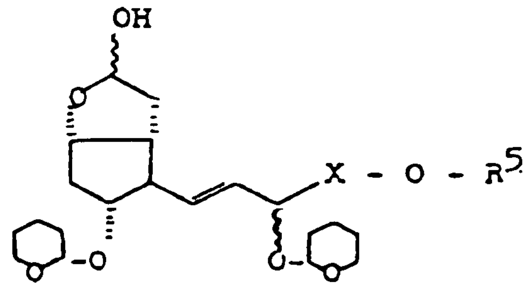
wherein X and R^5 have the same meaning as in formula I;

d) the obtained diol of formula VII is converted into a ditetrahydropyranyl ether of formula VIII by the acid-catalyzed addition of 2,3-dihydropyran:



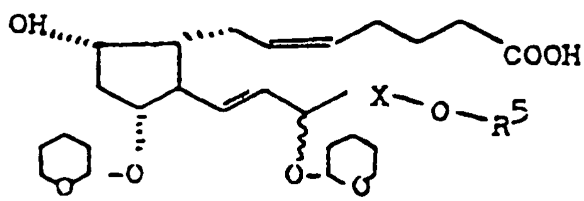
wherein X and R^5 have the same meaning as in formula I;

e) the obtained tetrahydropyranyl ether of formula VIII is reduced with a complex aluminum hydride in an aprotic solvent to form a lactol of formula IX:



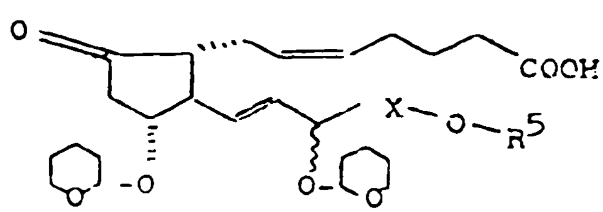
wherein X and R^5 have the same meaning as in formula I;

f) the obtained lactol of formula IX is reacted with the ylide from 4-carboxybutyltriphenylphosphonium bromide in a solution of sodium hydride in dimethyl sulfoxide in an inert atmosphere to form an acid of formula X:



wherein X and R^5 have the same meaning as in formula I;

g) optionally, the obtained compound of formula X is oxidized with an oxidation agent to form a compound of formula XI:



wherein X and R^5 have the same meaning as in formula I; and i) the tetrahydropyranyl protective groups in a compound of formula X or XI are split off by acidic hydrolysis and the obtained compound of formula I is optionally hydrogenated to form a compound of formula I, in which single bonds are present in the 5(6) and 13(14) positions, and if desired, the compound of formula I, in which either single or double bonds are present in both the 5(6) and 13(14) positions, is converted into a physiologically compatible salt or an ester.

Among the radicals mentioned for substituents X, the methylene and the ethylidene groups as well as the isomeric isopropylene and isobutylene groups, which are possible with respect to the linkage, and also the unsubstituted phenyl and benzyl radicals are preferred.

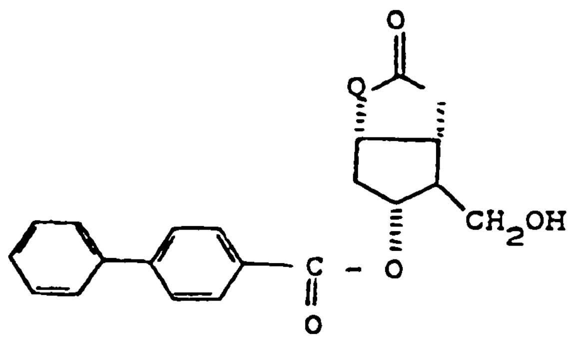
Among the groups mentioned for substituents R^5, the diphenyl ether group, which is substituted 1 to 3-fold, in one or both benzene rings with a halogen, in particular, with chlorine, and/or with an alkoxyl or alkyl with 1-3 C atoms, in particular, with methoxyl or methyl, and also the phenyl, benzyl, and the phenoxyalkyl groups with 2-4 C atoms in the straight-chain alkyl part, which are substituted 1-3-fold, in the ring with a halogen, in particular, with chlorine, and/or with an alkoxyl or alkyl with 1-3 C atoms, in particular, with methoxyl or methyl, are preferred. Particularly preferred are those of the aforementioned compounds that are substituted singly in the benzene ring with chlorine and/or with methoxyl.

The following groups are particularly preferred for R^5:

The 3-chloro-4-(4-chlorophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, 3-methoxy-4-(4-chlorophenoxy)phenyl, 3-chloro-4-(3-methoxy-4-chlorophenoxy)phenyl,

2-(3-chlorophenoxy)ethyl, 2-(3-chlorophenoxy)propyl, 3-chlorophenyl, 4-chlorophenyl, and 3-chloro-4-methoxyphenyl groups.

The method in accordance with the invention starts off with the aldehyde of formula III, which is produced according to Patent (Patent Application No. P 2,416,193.1 - HOE 74/F 096) from the primary bicyclic alcohol of formula II:



by oxidation with an oxidizing agent, such as with a complex of thioanisole and chlorine or the complex compound of CrO_3 and pyridine in an aprotic solvent at temperatures between -50°C and room temperature, preferably between -30°C and -5°C, in an inert atmosphere. For example, aromatic hydrocarbons, such as benzene or toluene, or for example, chlorinated aliphatic hydrocarbons, such as carbon tetrachloride, can be taken into consideration.

The obtained aldehyde of formula III is reacted according to Horner, Wittig, and Emmons with a phosphonic acid ester of formula IV to form an unsaturated ketone of formula V, wherein a preferred specific embodiment of the reaction consists in preparing the sodium salt of the phosphonic acid ester with sodium hydride in glycol dimethyl ether, subsequently adding an aldehyde of

formula III, and allowing the reaction to take place at room temperature for 2-6 h.

The phosphonic acid esters of formula IV can be prepared by reacting an ester of formula R^5-OX-CO_2-alkyl, in the presence of excess butyllithium and dimethyl methylphosphonate (for example, according to Corey, J. Am. Chem. Soc. Vol. 88, 5654 (1966)).

The epimeric mixture of the alcohols of formula VI is obtained from the ketone of formula V by reduction with a complex metal hydride, preferably with an alkali or zinc boronate in ethereal solution, preferably at temperatures between 0°C and room temperature. The zinc boronate is preferably prepared in-situ from zinc chloride and sodium boron hydride in absolute ethereal solution.

The alcohols of formula VI are particularly suitable for a separation into S- and R-epimers, preferably by means of column chromatography on silica gel, but the further reaction can also be carried out with the epimeric mixture, and epimer separation can be undertaken at the stage of the end product.

The subsequent hydrolytic splitting off of the p-phenylbenzoyl group of the alcohol of formula VI is carried out in an alcoholic medium with the aid of alkali metal or alkaline-earth metal carbonates. An advantageous specific embodiment is to be found in treating the alcohol or the corresponding epimeric mixture in absolute methanol at room temperature with anhydrous potassium carbonate, wherein the diol of formula VII is formed.

The preparation of the ditetrahydropyranyl ether of formula VIII takes place in an ethereal or benzene solution of the alcohols of formula VII, in the presence of the usual acidic catalyst, such as toluenesulfonic acid.

The compound of formula VIII is reduced with a complex aluminum hydride in an aprotic solvent to form a lactol of formula IX. The work is preferably carried out with diisobutyl aluminum hydride in toluene at -60°C to -70°C.

The obtained lactone of formula IX can be reacted, without further purification, according to Wittig, to form a carboxylic acid of formula X. The preferred specific embodiment follows the instructions given in J. Org. Chem. Vol. 28, 1128 (1963).

For the preparation of a prostaglandin of the E series, a compound for formula X is oxidized at temperatures of -40° to 0°C, preferably with a Jones reagent (solution of chromium(VI) oxide in sulfuric acid) in acetone or a complex compound of chromium(VI) oxide with pyridine in methylene chloride as a solvent at -20°C. The obtained compound of formula XI is separated by extraction and if required, purified by column chromatography.

The splitting off of the ether protective groups in a compound of formula X or XI takes place by a gentle acidic hydrolysis of the tetrahydropyranyl ether groups with aqueous organic acid, preferably in 2% aqueous-alcoholic oxalic acid solution at 20-50°C, or by heating for 1-2 h in 60-70% acetic acid at 40°C, wherein a carboxylic acid of formula I, in which a double bond is present in the 5(6) and 13(14) positions, is formed.

For the preparation of a prostaglandin of the tetrahydro-E or tetrahydro-F series, a compound of formula I with Δ5(6) and Δ13(14) double bonds is hydrogenated in the presence of a noble metal catalyst, wherein a compound of formula I with a single bond both in the 5(6) as well as in the 13(14) position is formed. In a preferred specific embodiment, hydrogenation is carried out at room temperature, in an alcoholic solution, in the presence of a catalyst consisting of 5% palladium on carbon.

If epimer separation does not take place at the stage of the alcohols of formula VI, a separation of the 15S- from the 15-epimer is preferably undertaken at the stage of a compound of formula I, wherein R_1 and R_2 together denote oxygen or a compound of formula I, wherein R_1 and R_2 are different, and each denotes hydrogen or the hydroxyl group. Separation preferably takes place on silica gel (Merck®, 70-230 mesh), wherein the 15S-epimer is mostly eluted after the 15R-epimer.

Suitable as elution agents for column chromatographic separation of the compounds of formula I, wherein R_1 and R_2 together denote oxygen, are mixtures of chloroform and methanol in a ratio 15:1 to 3:2, or a mixture of cyclohexane, ethylacetic acid and glacial acetic acid in a ratio 40:60:1, wherein the separation of compounds of formula I, wherein R_1 and R_2 are different and each denotes H or OH, preferably with a mixture of ethylacetic acid and acetic ester in a ratio 97.5:2.5.

According to the method of the invention, it is possible to produce, in particular, the following compounds also, in addition to the ones mentioned in the examples:

9S,11S,15-trihydroxy-16,16-dimethyl-16-(4-(4-chlorophenoxy)phenoxy)-5-cis,13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16-methyl-16-(4-(4-chlorophenoxy)phenoxy)-5-cis,13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16-(3-methoxy-4-(4-chlorophenoxy)phenoxy)-5-cis,13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16-methyl-16-(2-(3-chlorophenoxy)ethoxy)-5-cis,13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16-(2-(3-chlorophenoxy)propoxy)-5-cis,13-trans-tetranorprostadienoic acid

9S,11S, 15-trihydroxy-16,16-dimethyl-(3-chloro-4-(3-methoxy-4-chlorophenoxy)phenoxy-5-cis,13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16-(2-(3-chlorophenoxy)ethoxy)-5-cis, 13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-15-(4-(3-chlorophenoxymethyl)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-15-(4-(4-chlorophenoxymethyl)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-15-(4-(benzyloxy)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-15-(4-(3-chlorobenzyloxy)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-15-(4-(4-methylbenzyloxy)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-15-(3-chloro-4-(benzyloxy)phenyl)-5-cis, 13-trans-pentanorprostadienoic acid

9S, 11S, 15-trihydroxy-16-(2-(3,4,5-trichlorophenoxy)ethoxy)-5-cis, 13-trans-tetranorprostadienoic acid

9S, 11S, 15-trihydroxy-16-(2-(2,4-dichloro-3-methylphenoxy)ethoxy)-5-cis, 13-trans-tetranorprostadienoic acid

9S, 11S, 15-trihydroxy-16-(2-(2,4-dibromo-3-methylphenoxy)ethoxy)-5-cis, 13-trans-tetranorprostadienoic acid

9S,11S,15-trihydroxy-16,16-dimethyl-16(3-methoxy-4-(2,4-dichlorophenoxy)phenoxy)-5-cis,13-trans-tetranorprostadienoic acid

Of the aforementioned F-type prostaglandins (in the experimental part, Example 8), it is also possible to produce the corresponding E-type prostaglandins (Example 10) and the corresponding tetrahydro derivatives of the F-type prostaglandins (Example 11) and the corresponding tetrahydro derivatives of the E-type prostaglandins (Example 12).

The compounds of general formula I, in accordance with the invention, do not represent non-naturally occurring analogs of prostanoic acids, which can be used as medicines because of their pharmacological effects.

The natural prostaglandins $PGE_{1\alpha}$, $PGE_{2\alpha}$, $PGF_{2\alpha}$, or PGA_2 have the disadvantage that they are so rapidly deactivated in the living body that they cannot maintain their pharmacological effect during the time required for the therapy.

In contrast to this, the compounds in accordance with the invention are characterized by a longer period of effectiveness and a stronger effect.

The compounds in accordance with the invention can be used as medicines with blood pressure-lowering and diuretic effects, prophylactic and therapeutic effects with thromboses, birth-inducing effect, as abortifacients, contraceptives, as agents for the inhibition of gastric juice secretion, and as agents against stomach ulcers and against asthma. In particular, the compounds in accordance with the invention are suitable as contraceptives for use in humans and also for the synchronization of the estrus cycle with various species of animals.

They can be used as a free acid, in the form of their physiologically safe inorganic or organic salts or as esters of aliphatic, cycloaliphatic, or arylaliphatic alcohols. As salts, one can, for example, take into consideration benzyl ammonium, triethyl ammonium, or morpholine salts and alkali metal salts, as esters, preferably the esters of saturated, branched or unbranched, lower aliphatic alcohols, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or pentyl esters and benzyl ester.

Acids, as salts or esters, can be used in the form of their aqueous solutions or suspensions or also as solutions in pharmacologically safe organic solvents, such as mono- or multivalent alcohols, dimethyl sulfoxide or dimethylformamide, also in the presence of pharmacologically safe polymer carriers, such as polyvinylpyrrolidone.

As preparations, one can consider the usual galenic infusion or injection solutions and tablets, and topically applicable preparations, such as creams, emulsions, suppositories, or aerosols.

The compounds can be used alone or together with other pharmacological active substances, such as diuretics or antidiabetics.

The compounds of formulas V, VI, VII, VIII, IX, X, XI are valuable intermediate products for the synthesis of the compounds of formula I, in accordance with the invention.

Example 1:

a) Synthesis of dimethyl-2-oxo-3-methyl(3-chloro-4-(4-chlorophenoxy)phenoxy)propylphosphonate (IVa)

18.5 g dimethylmethylphosphonate were cooled to -70°C, under argon, in 200 mL tetrahydrofuran. While stirring, 50 mL of a 20% n-butyllithium solution in hexane were added. After 45 min, 18.0 g 4-(4-chlorophenoxy)-3-chlorophenoxypropionate-2-methyl ester in 50 mL tetrahydrofuran were added at 70°C. Then, 2 h of stirring were carried out. Neutralization with glacial acetic acid followed. The solvent was concentrated in a vacuum; the residue was taken up

in chloroform and washed with water; the chloroform phase was dried with Mg/SO_4, concentrated; and the residue was purified by means of column chromatography.

Column: Silica gel (Merck, 70-230 mesh), elution agent benzene:ethylacetic acid = 4:1, after approximately 100 fractions benzene:ethylacetic acid = 1:1.

Fractions 160-250 contained:
7.5 g slightly yellow oil (IVa) (34%)

Elemental analysis:	C	M	P
Calculated $C_{18}H_{19}PO_6Cl_2$	50.1	4.4	7.1
Found	50.2	4.2	7.2

Nuclear magnetic resonance (in $CDCl_3$) δ values:
1.55 doublet 3 H (CH_3), 3.3 doublet 2 H ($CO-CH_2-P(o)<$) J = 22 H_2,
3.8 doublet 6 H (OCH_3), 4.8 quartet 1 H ($CH-CH_3$),
6.7-7.4 multiplet 7 H (aromatic protons).

IVb was produced in the same manner.

b) Dimethyl-2-oxo-3-dimethyl-3-(4-(4-chlorophenoxy)phenoxy)propylphosphonate (IVb)

23 g dimethylmethylphosphonate, produced
with
62 mL 20% butyllithium solution in hexane and with
25.4 g 4-(4'-chlorophenoxy)-2-phenoxyisobutyric acid methyl ester,
36.8 g light yellow oil.
Column chromatography with SiO_2 (Merck, 70-230 mesh)
Elution agent benzene:ethylacetic acid = 4:1 produced, in fractions 96-285,

23 g almost colorless oil (89%) IVb, which crystallizes in the refrigerator. Melting point 72°C

Elemental analysis:	C	H	P
Calculated for $C_{19}H_{22}PO_6Cl$	55.3	5.4	7.5
Found	54.9	5.6	7.3

Nuclear magnetic resonance (in $CDCl_3$) δ values:
1.55 singlet 6 H (CH_3), 3.5 doublet 2 H (CO_2-CH_2-P(o)<) J = 22 H_2, 3.85 doublet 6 H (OCH_3), 6.8-7.4 multiplet 8 H (aromatic protons).

Example 2

a) Synthesis of 2-oxa-3-oxy-6-(3-oxo-4-methyl-4-(3-chloro-4-(chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Va)

7.0 g phosphonate IVa were added in drops, under argon and within 15 min, to a sludge of 0.67 g sodium hydride (80% suspension in oil) in 150 mL absolute 1,2-dimethoxyethane. A dissolution begins with the evolution of hydrogen. Stirring is carried out for 40 min and then 4.9 g lactone aldehyde III in 75 mL DME are added in drops within 10 min. Stirring is carried out for another h, followed by neutralization with glacial acetic acid; clarification is undertaken with animal charcoal, followed by filtration and concentration in a vacuum. The residue is mixed with 80 mL isopropanol, followed by stirring and suctioning. 6.1 g of the desired product were hereby obtained (Va).
Yield: 65% Melting point 139°C

Elemental analysis:	C	H	P
Calculated for $C_{37}H_{30}O_7Cl_2$	67.4	4.6	10.1
Found	66.8	4.5	10.1

Nuclear magnetic resonance (in $CDCl_3$) δ values:
1.5 doublet 3 H (CH_3), 2.2-3.2 multiplet 6 H (-CH_2-,-CH-)
4.4-5.3 multiplet 3 H (-O-CH-CH_3, -CH-O-CO-), 6.2-6.6 multiplet 2 H (olefinic protons), 6.8-8.2 multiplet 16 H (aromatic protons)

Thin-layer chromatogram: (developer solution:methylene chloride methanol 4:1); silica gel (Merck)
R_f = 0.80

b) Synthesis of 2-oxa-3-oxy-6-(3-oxo-4,4-dimethyl-4-(4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vb)

Analog V a was refined to 15.2 g of compound IVb and reacted with 10.1 g lactone aldehyde III. After regeneration, we obtained, as compound (V b), 13.2 [g] white crystals of melting point 157° (62%).

Elemental analysis:	C	H	Cl
Calculated for $C_{38}H_{33}O_7Cl$	71.8	5.2	5.6
Found	70.8	5.4	4.9

Nuclear magnetic resonance (in $CDCl_3$) δ values:
1.4 doublet 6 H (CH_3), 2.2-3.2 multiplet 6 H (-CH_2-,-CH-)
4.6-5.4 multiplet 2 H (-CH-O-CO-), 6.4-8.2 multiplet 19 H (olefinic protons, aromatic protons).

Thin-layer chromatogram: (developer solution:methylene chloride-methanol 4:1)

R_f = 0.84

The following were prepared analogously:

c) 2-oxa-3-oxy-6-(3-oxo-4-methyl-4-(4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vc)

d) 2-oxa-3-oxy-6-(3-oxo-4-(3-methoxy-4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vd)

e) 2-oxa-3-oxy-6-(3-oxo-4-methyl-4-(2-(3-chlorophenoxy)ethoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Ve)

f) 2-oxa-3-oxy-6-(3-oxo-4-(2-3-chlorophenoxy)propoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vf)

g) 2-oxa-3-oxy-6-(3-oxo-4,4-dimethyl-4-(3-chloro-4-(3-methoxy-4-chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vg)

h) 2-oxa-3-oxy-6-(3-oxo-4-(2-(3-chlorophenoxy)ethoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vh)

i) 2-oxa-3-oxy-6-(3-oxo-3-(4-(3-chlorophenoxymethyl)phenyl)-1-propenyl-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vi)

k) 2-oxa-3-oxy-6-(3-oxo-3-(4-(4-chlorophenoxymethyl)phenyl)-1-propenyl-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vk)

l) 2-oxa-3-oxy-6-(3-oxo-3-(4-benzyloxy)phenyl)-1-propenyl-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vl)

m) 2-oxa-3-oxy-6-(3-oxo-3-(4-(3-chlorobenzyloxy)phenyl)-1-propenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vm)

n) 2-oxa-3-oxy-6-(3-oxo-3-(4-methylbenzyloxy)phenyl-1-propenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vn)

o) 2-oxa-3-oxy-6-(3-oxo-3-(3-chloro-4-(benzyloxy)phenyl)-1-propenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vo)

p) 2-oxa-3-oxy-6-(3-oxo-4-(2-(3,4,5-trichlorophenoxy)ethoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vp)

q) 2-oxa-3-oxy-6-(3-oxo-4-(2-(2,4-dichloro-3-methylphenoxy)ethoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vq)

r) 2-oxa-3-oxy-6-(3-oxo-4-2-(2,4-dibromo-3-methylphenoxy)ethoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vr)

s) 2-oxa-3-oxy-6-(3-oxo-4,4-dimethyl-4-(3-methoxy-4-(2,4-dichlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (Vs)

The other reactions were carried out, proceeding from compounds (Va) to (Vs), in an analogous manner. In Examples 3-12, below, however, only the reactions which begin with compound Va are described in a detailed manner.

Example 3:

Synthesis of 2-oxa-3-oxy-6-(3-hydroxy-4-methyl-4-(3-chloro-4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-(4-biphenylcarbonyloxy)bicyclo[3.3.0]octane (VI)

6.1 g of compound Va were dissolved in 95 mL 1,2-dimethoxy ethane. At 0°C, 30 mL of a 0.5M zinc boron hydride solution (prepared as follows: 2.8 g zinc chloride suspended in 45 mL 1,2-dimethoxy ether and while cooling and stirring, 1.52 g sodium boron hydride added; stirred for 0.5 h and filtered off rapidly, under argon, from undissolved matter) were added. At room

temperature, stirring was carried out for 2.5 h. Then excess reagent was decomposed at 0°C with glacial acetic acid. The desired product was extracted with ethylacetic acid-water. The organic phase was dried with $MgSO_4$, filtered, and concentrated n a vacuum.

The yield of compound VI was:

5.1 g colorless oil (76%).

By column chromatography with pure diethyl ether, it was possible to separate the 15S- and 15R-epimers readily.

R_f value for the 15S-epimer in a thin-layer chromatogram (silica gel Merck):

(Flow path of the solvent front 30 cm)

(Ether) = 0.33

R_f value for the 15R-epimer

= 0.25

Absorptions in the infrared spectrum (without solvent): 3455 (OH band), 2920, 1778 (lactone carbonyl), 1720 (ester carbonyl)

Example 4:

Synthesis of 2-oxa-3-oxy-6-(3-hydroxy-4-methyl-4-(3-chloro-4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-hydroxybicyclo[3.3.0]octane (VII)

4.9 g of compound VI were dissolved in 120 mL absolute methanol; at room temperature, 1.5 g very finely pulverized potassium carbonate were then added and stirred under argon for 2.5 h. p-diphenylcarboxylic acid methyl ester precipitated thereby as a crystalline deposit. With ice cooling, with it was acidified

to pH 21N hydrochloric acid; the p-diphenylcarboxylic acid methyl ester was suctioned off and the filtrate was mixed with ethylacetic acid-water. The organic phase was separated after the extraction, dried with $MgSO_4$, and the solvent, removed in a vacuum. The yield of compound VII was 3.4 g colorless oil (86%).
Thin-layer chromatogram (silica gel, Merck) (developer solution: methanol-chloroform = 2:8) - phosphorous molybdic acid as the spray reagent
R_f = 0.67

Example 5:

Synthesis of 2-oxa-3-oxy-6-(3-tetrahydropyranyloxy-4-methyl-4-(3-chloro-4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]octane (VIII)

3.8 g of compound VII were dissolved in 100 mL absolute methylene chloride; then 7.5 g 2,3-dihydropyran and 1 mL of a 0.5% solution of p-toluenesulfonic acid in methylene chloride were added. Stirring was carried out at room temperature for 3 h; then ethylacetic acid was added and mixed with saturated sodium bicarbonate solution. The organic phase was separated, dried with magnesium sulfate; the solvent was removed in a vacuum. The residue (7.2 g colorless oil) was subjected to a column chromatography on silica gel (Merck 70-230 mesh), elution agent benzene:ethylacetic acid = 6:1. Fractions 96-190 contained 2.05 g compound VIII as a colorless oil (41%).

Thin-layer chromatogram (developer solution:benzene-ethylacetic acid (4:1)

R_f = 0.25

Nuclear magnetic resonance (in $CDCl_3$) δ values:

1.3 doublet 3 H (CH_3), 1.1-1.9 multiplet 12 H (THP-CH_2) 1.9-2.9 multiplet 6 H (-CH_2-, -CH-), 3.2-4.3 multiplet 7 H (-CH-O-, -CH_2-O-), 4.4-4.7 multiplet 2 H

(//ins p 22//)

4.8-5.1 multiplet 1 H (-CH-O-CO-), 5.4-5.7 multiplet 2 H olefinic protons, 6.6-7.4 multiplet 7 H (aromatic protons)

Example 6

Synthesis of 2-oxa-3-hydroxy-6-(3-tetrahydropyranyloxy-4-methyl-4-(3-chloro-4-(4-chlorophenoxy)phenoxy)-1-butenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]octane (IX)

2.1 g of compounds VIII were dissolved in 25 mL toluene; then cooling to -70°C was carried out and 8 mL of a 1.2M solution of diisobutyl aluminum hydride in toluene were added in drops within 3 min under an argon atmosphere. The mixture was stirred for 2 h at -70°C; then excess hydrogenation reagent was decomposed with 10 mL methanol. The reaction product is extracted with ethylacetic acid and semisaturated sodium chloride solution. The organic phase was separated, dried with magnesium sulfate, and the solvent was removed in a vacuum. The yield of compound (IX) was 1.2 g colorless oil (59%).

Thin-layer chromatogram (developer solution:benzene-ethylacetic acid 4:1)
R_f = 0.06
Absorptions in the infrared spectrum (without solvent): 3400 (OH = band), 2930, no carbonyl band

Example 7:

Synthesis of 9S-hydroxy-11S,15-SR-bistetrahydropyranyloxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)-5-cis-13-trans-tetranorprostadienoic acid (X.)

0.43 g sodium hydride (80% suspension in oil) was mixed with 10 mL absolute dimethyl sulfoxide, under argon, and stirring was carried out for 1 h at 60°C, until the development of hydrogen ceased. After cooling to room temperature, 2.85 g 4-carboxytriphenyl phosphonium bromide (dried at 120°C in a high vacuum), dissolved in 10 mL absolute dimethyl sulfoxide, were added in drops to this solution. The phosphorylide needed for the Wittig reaction formed with intensive red coloring. Stirring is carried out at 30°C for another 30 min.

Then, 1.2 g of compound IX in 5 mL dimethyl sulfoxide were added in drops. Stirring was carried out at room temperature for 2.5 h and subsequently placed in ice water, which was covered with a layer of diethyl ether. The neutral substances are first extracted and then the aqueous solution is acidified with 5% sodium bisulfate solution with ice water cooling to pH 2 and immediately extracted with ether. The ether solution is then extracted with 0.5N sodium hydroxide; the aqueous alkaline phase is separated and again acidified with ice cooling and extracted with ether; the

ether solution was dried with magnesium sulfate, filtered and concentrated in a vacuum. According to column chromatography on 250 g silica gel (solvent system: ethylacetic acid-acetic acid 97.5:2.5), the yield of compound IX was
1.2 g light yellow oil (90%).
Thin-layer chromatogram (developer solution: ethylacetic acid-acetic acid 97.5:2.5)
$R_f = 0.57$
Absorptions in the infrared spectrum (without solvent): 3400 (OH band), 2950, 1715 (carbonylband)

Example 8:

Synthesis of 9S,11S,15-trihydroxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)-5-cis-13-trans-tetranorprostadienoic acid (IA)

15S- and 15R-epimers ($PGF_{2\alpha}$ type)

1.2 g of compound X were dissolved in 10 mL tetrahydrofuran; then 10 mL 0.5N hydrochloric acid were added and stirring was carried out, under argon, at 40°C for 3 h. Extraction is subsequently carried out with chloroform-water. The organic phase was dried with $MgSO_4$ and the solvent was removed in a vacuum. A raw yield in IA of 1.3 g (light yellow oil) was produced.

The subsequent column chromatography with ethylacetic acid-acetic acid 97.5:2.5 (on 180 g silica gel (Merck, 70-230 mesh)) produced the following in the fractions (individual fractions:

4 mL):

17-18 256 mg 15R-epimer IA, and in

fractions

29-70 200 mg 15S-epimer IA

Yield: 0.456 g (49%)

Thin-layer chromatogram (solvent as with column chromatography)

15R-epimer $R_f = 0.33$

15S-epimer $R_f = 0.24$

Nuclear magnetic resonance (in $CDCl_3$) δ values: (Spectra for the 15R- and the 15S-epimer within the framework of the usual dissolution, practically identical).

1.15 doublet 3 H (CH_3), 1.0-2.6 multiplet 12 H ($-CH_2-$, >CH-), 3.6-4.4 multiplet 4 H (-CH-O-), 5.2-5.7 multiplet 4 H (olefinic H), 5.6-6.2 multiplet 4 H (OH,COOH), 6.7-7.3 multiplet 7 H (aromatic protons)

The multiplet can be removed between 5.6-6.2 ppm by H/D exchange.

<u>Example 9:</u>

Synthesis of 9-oxo-11S,15-bistetrahydropyranyloxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)-5-cis-13-trans-tetranorprostadienoic acid (XI)

0.83 g of compound X is dissolved in 30 mL acetone. At -20 to -25°C, 2 mL Jones reagent (2.1 g chromic acid, 6 mL water, 1.7 mL concentrated sulfuric acid) are added in drops, under argon. Stirring is carried out for 30 min; 3 mL isopropanol are then added, followed by more stirring for 10 min, in order to destroy

the excess oxidation reagent. The mixture was then mixed with 100 mL methylene chloride and 100 mL water, shaken out; the phases were separated; the organic extract dried with $MgSO_4$; and the solvent, concentrated at a maximum +5°C in a vacuum. The yield of compound XI was
0.70 g light yellow, clear oil (85%)
Thin-layer chromatogram (ethylacetic acid-acetic acid = 97.5:2.5)
R_f = 0.60
Absorptions in the infrared spectrum (NaCl plates):
2950, 1745 (ketone-carbonyl), 1720 (acid-carbonyl)

Example 10:

Synthesis of 9-oxo-11-α-15-dihydroxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)-5-cis-13-trans-tetranorprostadienoic acid (IB)

15S- and 15R-epimer $PGE_{2\alpha}$ type

0.70 g of compound XI was dissolved in 5 mL tetrahydrofuran added to 15 mL acetic acid-water in a 2:1 ratio; and stirred at 40°C for 4 h. Then, the solvent was removed in a vacuum with the addition of benzene several times, wherein the temperature did not exceed +5°C. The yield in compound I B was 0.41 g light oil.

According to column chromatography on silica gel (Merck, 70-230 mesh) with chloroform-methanol = 22:1, the following was obtained in the fractions (individual fraction 2 mL):

150-190	120 mg	15R-epimer (IB) and in
fractions 195-310	112 mg	15S-epimer (IB)

Yield: 0.23 g (42%)
Thin-layer chromatogram (solvent: ethylacetic acid-acetic acid = 97.5:2.5) (silica gel, Merck)

R_f = 0.34 15R-epimer

R_f = 0.26 15S-epimer

The spectra for the 15R- and 15S-epimers of IB are, within the framework of the usual dissolution, practically identical.

Absorptions in the infrared spectrum (NaCl plates):
3450 (OH band), 2950, 1745 (ketone-carbonyl), 1720 (acid-carbonyl)

Example 11:

Synthesis of 9S,11S,15-trihydroxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)tetranorprostanoic acid (IC)

50 mg 5% palladium-animal charcoal catalyst were prehydrogenated in 5 mL ethanol for 1 h. Then 70 mg of compound IA (15 R-epimer) in 15 mL ethanol were added, and the hydrogenation was completed at room temperature for 3 h. The hydrogen intake was 12.5 mL. The mixture was filtered off from the catalyst, and the filtrate was concentrated in a vacuum.

Yield of compound IC:
65 mg colorless oil (94%)

Thin-layer chromatogram (ethylacetic acid-acetic acid 97.5:2.5)

R_f = 0.22 15R-epimer

(The same preparation was also carried out with the 15S-epimers of I A.)
Nuclear magnetic resonance (in $CDCl_3$) δ values:
1.13 doublet 3 H (CH_3), 1.0-2.8 multiplet 20 H ($-CH_2-$, >CH-),
3.6-4.4 multiplet 4 H (-CH-O-), 6.0-6.4 multiplet 4 H (OH, COOH),
6.7-7.3 multiplet 7H (aromatic protons).

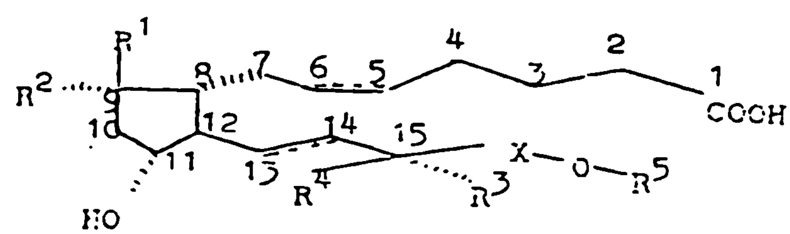
Example 12:

Synthesis of 9-oxo,11S,15-dihydroxy-16-methyl-16-(3-chloro-4-(4-chlorophenoxy)phenoxy)tetranorprostanoic acid (ID)

70 mg of compound IB were hydrogenated as under Example 11. 65 mg colorless oil (93%) were obtained.
Thin-layer chromatogram (ethylacetic acid-acetic acid 97.5:2.5)
R_f = 0.31

Claims

1. Compounds of formula I:



which comprise both the optically active compounds of the natural configuration, as well as the racemic compounds, and in which the meanings are as follows:

R^1 and R^2 together are oxygen or each is hydrogen or a hydroxyl group, wherein R^1 and R^2 are different;

R^3 and R^4 are each hydrogen or a hydroxyl group, wherein R^3 and R^4 are different;

X is a straight-chain or branched alkyl radical with 1-5 C atoms, or a phenyl or benzyl radical, which can be substituted 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms;

R^5, for the case in which X is a straight-chain or branched alkyl radical with 1-5 C atoms, is

a diphenyl ether, which is either unsubstituted or which is substituted 1 to 3-fold, in one or both rings with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxy, each with 1-4 C atoms, or a phenoxyalkyl radical, unsubstituted in the ring or substituted 1 to 3-fold, with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms, wherein the alkyl radical is straight-chain and contains 2-5 C atoms, or is branched and contains 3-6 C atoms;

or for the case in which X is a substituted or unsubstituted phenyl radical, is

a benzyl radical, which can be substituted 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxy, alkyl, and/or alkoxyl, each with 1-4 C atoms;

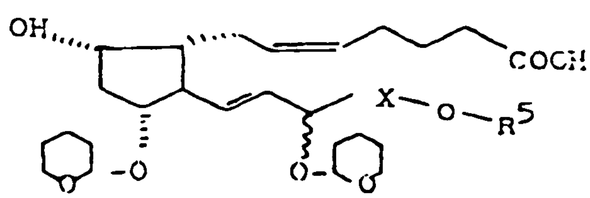
or for the case in which X is a substituted or unsubstituted benzyl radical, is

a phenyl radical, which can be substituted 1 to 3-fold, in the ring with a halogen, trifluoromethyl, hydroxyl, alkyl, and/or alkoxyl, each with 1-4 C atoms;

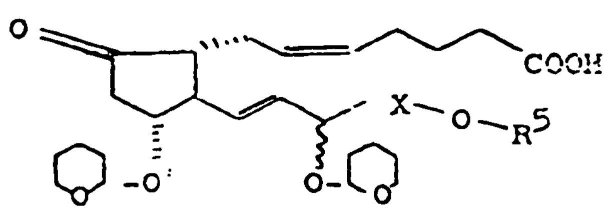
and wherein C atoms 5 and 6 and 13 and 14 are bound, either all by single bonds or all by double bonds,

and their physiologically compatible salts with organic and inorganic bases and their esters with aliphatic, cycloaliphatic, or arylaliphatic alcohols with 1-8 C atoms in the ester part.

2. Method for the production of compounds according to Claim 1, characterized by the fact that the tetrahydropyranyl protective groups in a compound of formula X:



or in a compound of formula XI:

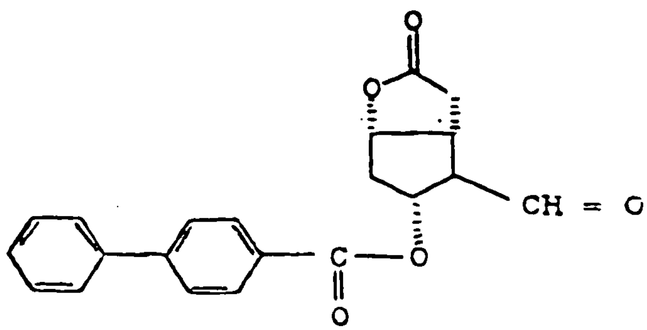


wherein X and R^5 have the same meaning as in formula I, are split off by acidic hydrolysis, and the obtained compound of formula I is optionally hydrogenated to form a compound of formula I, in which single bonds are present in the 5(6) and 13(14) positions, and if

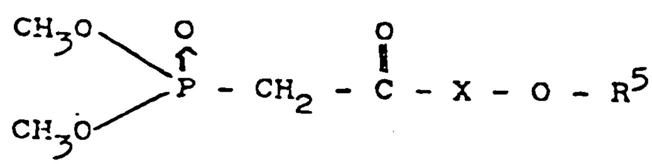
desired, the compound of formula I, in which either single or double bonds are present in both the 5(6) and 13(14) positions, is converted into a physiologically compatible salt or an ester.

3. Method according to Claim 2, characterized by the fact that for the production of compounds formula X or XI:

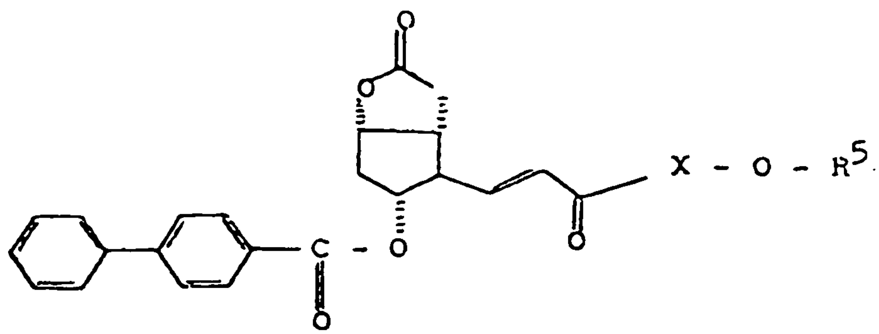
a) the aldehyde of formula III



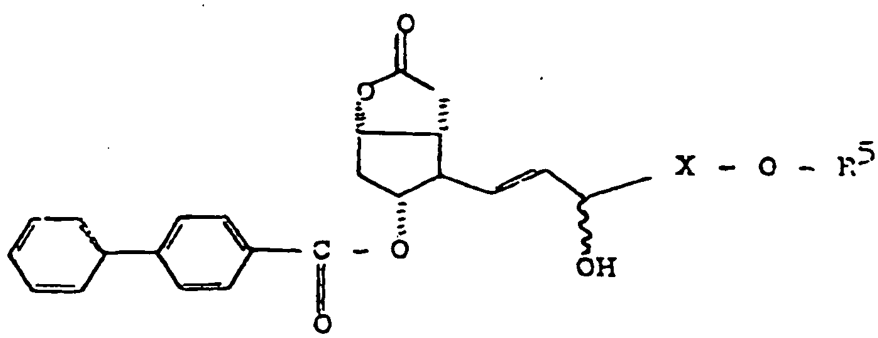
is reacted with a phosphonate of formula IV:



wherein X and R^5 have the same meaning as in formula I, to form an unsaturated ketone of formula V:

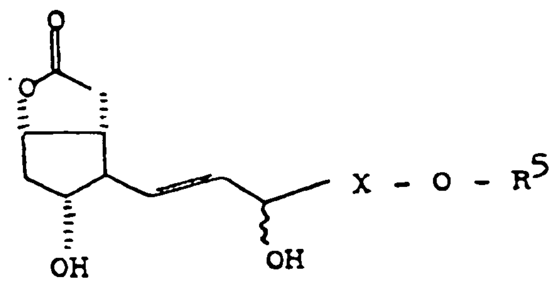


b) the obtained ketone of formula V is reduced with a complex metal hydride to form the epimeric mixture of alcohols of formula VI:



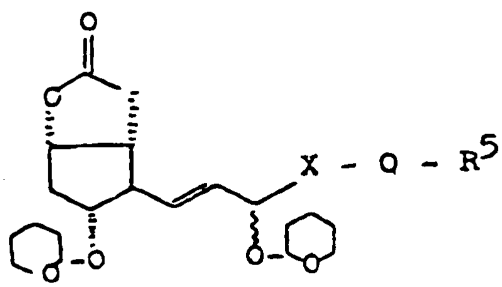
wherein X and R^5 have the same meaning as in formula I;

c) the alcohol of formula VI obtained as an epimeric mixture or after separation of the epimers, as a pure S- or R-epimer, is converted into a diol of formula VII with an anhydrous alkali metal or alkaline earth metal carbonate in an alcoholic medium at room temperature:



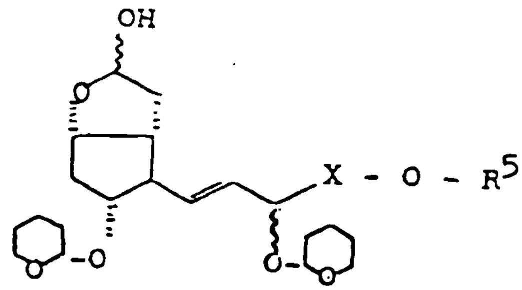
wherein X and R^5 have the same meaning as in formula I;

d) the obtained diol of formula VII is converted into a ditetrahydropyranyl ether of formula VIII by the acid-catalyzed addition of 2,3-dihydropyran:

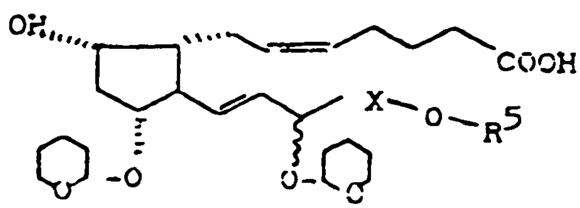


wherein X and R^5 have the same meaning as in formula I;

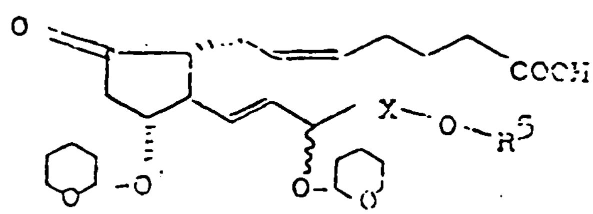
e) the obtained tetrahydropyranyl ether of formula VIII is reduced with a complex aluminum hydride in an aprotic solvent to form a lactol of formula IX:



wherein X and R^5 have the same meaning as in formula I;
f) the obtained lactol of formula IX is reacted with the xlide [sic; ylide] from 4-carboxybutyltriphenylphosphonium bromide in a solution of sodium hydride in dimethyl sulfoxide in an inert atmosphere to form an acid of formula X:

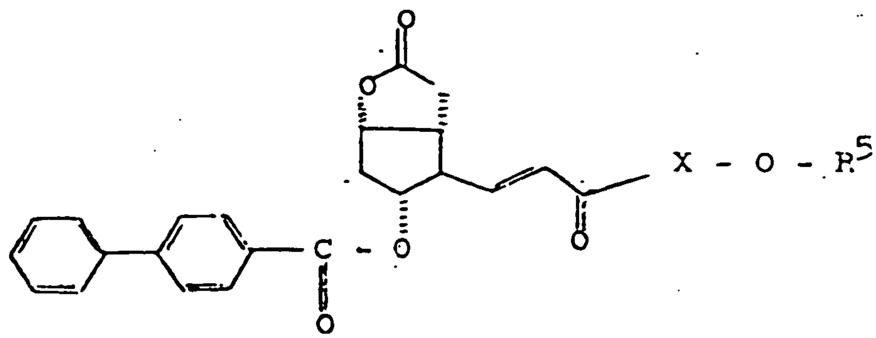


wherein X and R^5 have the same meaning as in formula I;
g) optionally, the obtained compound of formula X is oxidized with an oxidation agent to form a compound of formula XI:



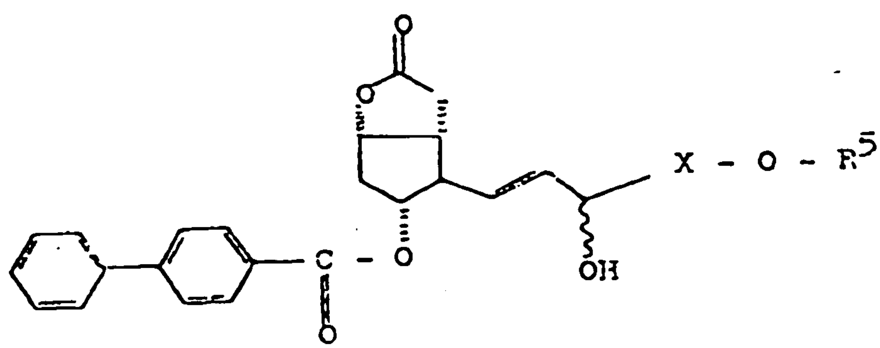
wherein X and R^5 have the same meaning as in formula I.

4. Compounds of formula V:



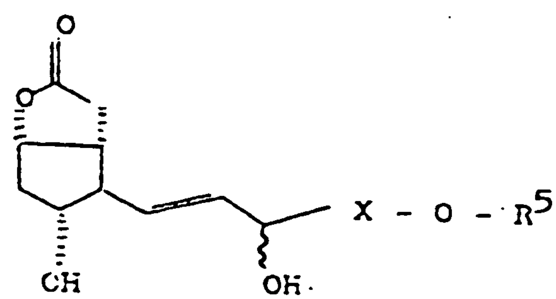
wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

5. Compounds of formula VI:



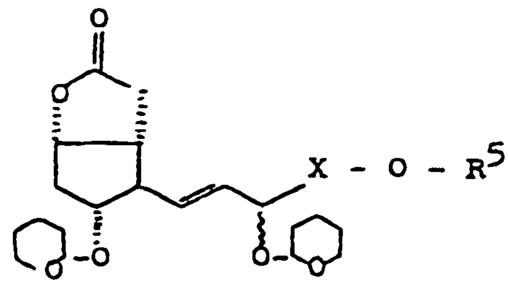
wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

6. Compounds of formula VII:



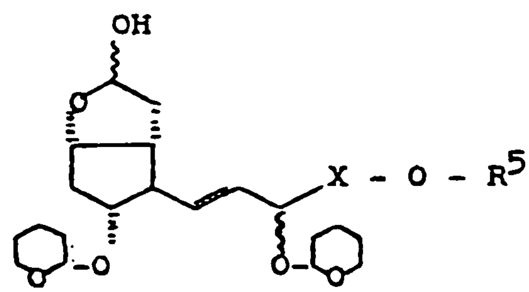
wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

7. Compounds of formula VIII:



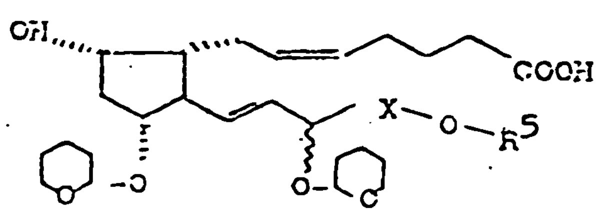
wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

8. Compounds of formula IX:



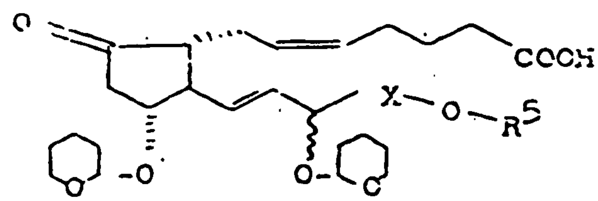
wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

9. Compounds of formula X:



wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

10. Compounds of formula XI:



wherein X and R^5 have the meaning mentioned in Claim 1 for formula I.

11. Method for the production of medicines, characterized by the fact that a compound of formula I, mentioned in Claim 1, is optionally brought into a therapeutically suitable application form with the usual pharmaceutical carriers and/or stabilizers.

12. Medicines, characterized by a content of a compound of formula I, mentioned in Claim 1, or consisting of such a compound.

13. Use of a compound of formula I, mentioned in Claim 1, in medicines or as a medicine.